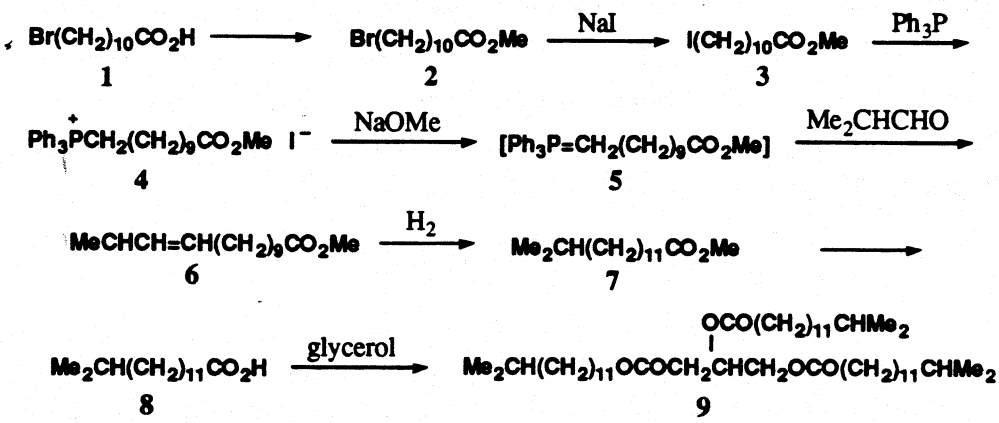
AN EFFICIENT, LARGE-SCALE SYNTHESIS OF TRIISOPENTADECANOIN

Thomas A. Foglia* and Peter D. Vail

Eastern Regional Research Center
Agriculture Research Service, U. S. Department of Agriculture
600 East Mermaid Lane, Philadelphia, PA 19118

Large quantities of triisopentadecanoin [tri-(13-methyltetradecanoyl)-glycerol] (**9**) were needed for studies dealing with the direct incorporation and release of dietary fatty acids in the adipose tissue of poultry. To this end, a facile synthesis of 13-methyltetradecanoic acid (**8**) was required. A search of the literature indicated several reasonable routes to isoacid **8**: a) electrolysis of a mixture of an isocarboxylic acid and a half acid ester of an α,ω-dicarboxylic acid in anhydrous methanol solution,[1] b) the coupling of a terminal alkyne with an ω-halocarboxylic acid[2] followed by hydrogenation of the alkynoic acid and c) the Wittig reaction of an alkylphosphonium salt with a carbonyl compound,[3] with subsequent hydrogenation of the resultant alkenoic acid. The Wittig reaction was selected because of the availability and/or facile synthesis of required intermediates and its apparent ease in scale-up.

Although this approach appeared to be the method of choice, difficulties were encountered in its implementation. For example, the choice of solvent and/or the source of alkoxide often caused variable results which became even more problematic on scale-up and thus the yields were quite



variable. Moreover, alkenoate ester **6** obtained from the condensation of phosphorane **5** and the carbonyl component was contaminated with triphenylphosphine oxide by-product which introduced a separation problem. Finally, the last step to the titled compound **9** was fraught with complications, the

most notable of which was incomplete reaction and formation of partial glycerides. It was felt that a better understanding of the steps shown in the Scheme and in particular of the variables in the reaction sequence was needed before scale-up to the desired level. The procedures described herein overcame these problems.

The key step to **8** was the condensation of isobutyraldehyde with phosphorane **5**. The latter was generated *in situ* from phosphonium ylide **4** and sodium methoxide in anhydrous DMF. This condensation reaction gave the unsaturated ester **6** which after hydrogenation and saponification gave the required isopentadecanoic acid **8**.

Our initial approach was to use the ylide obtained from the reaction of 11-bromoundecanoic acid (**1**) and triphenylphosphine. The latter ylide (a glassy liquid which would not crystallize) when treated with two equivalents of sodium methoxide in DMF and isobutyraldehyde gave poor yields of the condensation product (~15% as determined by glc of methyl ester **6**). Similarly, methyl ester **2** yielded a non-crystallizable ylide, which also gave variable and low yields of the alkenoate methyl ester **6**. In contrast, good yields were consistently obtained when phosphonium iodide salt **4** was used to prepare phosphorane **5**. Reaction of ylide **4**, readily obtained from iodo ester **3** as a crystalline solid, with sodium methoxide consistently gave a solution with a bright orange-red color that dissipated rapidly upon the addition of isobutyraldehyde to form unsaturated ester **6** in yields in excess of 85% as determined by glc. As previously noted,[4] the source of sodium methoxide used to generate the Wittig reagent can adversely affect yield of alkenes. The best results were obtained when the sodium methoxide base was freshly prepared. Separation of **6** from phosphine oxide was readily accomplished by triturating the crude product with hexane in which the oxide has limited solubility. After removal of Ph_3PO, distillation gave pure **6** as a 95:5 mixture of *cis/trans* isomers.[5] Subsequent hydrogenation and saponification of **6** yielded the desired isoacid **8**.

The esterification of acid **8** with glycerol to triglyceride **9**, was complicated by the incompleteness of the reaction which led to significant amounts of mono- and diglycerides in the product mixture (as determined by tlc). In order to drive this reaction to completion, it was necessary to conduct it at 150° and at a pressure of < 50 mm Hg using equipment that ensured complete removal of water of reaction (see Experimental Section). In this manner glyceride **9** was obtained in > 98% crude yield; it was then purified by column chromatography. This sequence of reactions allowed the preparation of **9** in single batches of > 100 gram with an overall yield of 55% starting from **1**.

EXPERIMENTAL SECTION[6]

All chemicals and solvents were reagent grade or better. IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer using 3% solutions in CCl_4. ^1H NMR spectra were determined on a Jeol 400 MHz spectrometer in $CDCl_3$ solutions. Chemical shifts are reported in δ, ppm relative to TMS. Mass spectra were determined on a Hewlett-Packard 5995 GC-MS system interfaced with an OV-1 capillary column (0.25 mm ID x 12m). Gas liquid chromatography (glc) was accomplished using a Hewlett-Packard 5990 gas chromatograph equipped with an SP-2330 column (25 mm ID x 30m) with flame ionization detection and split capillary injector. The carrier gas was He set at a 50:1 split ratio.

Thin layer chromatography (tlc) was performed using silica gel G (0.25 mm, 5 x 20 cm) plates from Analabs, Inc. Plates were developed with hexane:ether:formic acid (80:20:2) and visualized by spraying with 3% cupric acetate in 8% orthophosphoric acid and heating at 120° for 1 hr. Column chromatography was conducted on silica gel, Merck, Grade 60, 200-400 mesh, 60Å.

Methyl 11-Iodoundecanoate (3).- 11-Bromoundecanoic acid (100 g, 0.38 mole) was converted to its methyl ester **2** by refluxing in methanol:toluene (1:2, 450 mL) in the presence of *p*-toluenesulfonic acid (1.0 g) for 8 hrs, washing in sequence with 5% sodium bicarbonate solution (50 mL), water (3 x 200 mL), and satd. salt solution (50 mL). The solvent was removed *in vacuo* to give bromo ester **2** in 96% yield as determined by glc. Distillation gave pure methyl 11-bromoundecanoate (92%), bp. 112-115°/0.3 mm Hg. Bromo ester **2** (70 g, 0.25 mole) was added to a solution of sodium iodide in acetone (500 mL) and the mixture was heated at reflux for 4 hrs. The mixture was filtered to remove precipitated NaBr and the acetone solvent removed *in vacuo*. The residual semi-solid was triturated with warm hexane, filtered and the hexane solution cooled to -20° and the precipitated solid was collected to give 75.2 g (78%) of iodo ester **3**. Recrystallization of **3** from hexane at -10° gave cream crystals, mp. 27.5-28.5°.

Anal. Calcd for $C_{12}H_{23}IO_2$: C, 44.18; H, 7.11; I, 38.90. Found: C, 44.32; H, 7.15; I, 38.60

1-Decyl-[10-carbomethoxy]-triphenylphosphonium Iodide (4).- To a solution of iodo ester **3** (163 g, 0.5 mole) in acetonitrile (500 mL) was added triphenylphosphine (144 g, 0.55 mole). The mixture was refluxed for 18 hrs, cooled and the solvent removed *in vacuo* to give an orange glassy mass. The latter was dissolved in hot acetone (500 mL), cooled to room temp. and ether (300 mL) was added; the solution was allowed to stand at room temp., then cooled to 0° for 1 hr and then to -20° for 16 hrs. The fine white crystals were collected and washed with ether to give **4**, 249 g (85%), mp. 128-130°, lit.[7] mp. 128-130°.

Methyl 13-methyltetradec-11-enoate (6).- Sodium metal (7.5 g, 0.326 g/atom) was reacted with anhy. MeOH (100 mL) in a 1 L Morton flask. When reaction was complete, the excess methanol was evaporated *in vacuo*, the residual sodium methoxide suspended in anhy. dimethylformamide (DMF) (50 mL) and phosphonium salt **4** (192 g, 0.323 mole) in DMF (250 mL) was added over a period of 45 min. The resultant orange-red mixture was then heated at 40° for 15 min and isobutyraldehyde (23.8 g, 0.33 mole) in DMF (50 mL) was added over 30 min. and the reaction allowed to stand for 1 hr at room temp. The mixture was acidified with 10% HCl to pH 1, and H_2O (500 mL) was added. The organic products were extracted with Et_2O (4x200 mL) and the combined organic layers washed with H_2O (2x75 mL), satd. NaCl (75 mL) and dried over anhy. $MgSO_4$. The drying agent was filtered and the Et_2O removed from the filtrate *in vacuo*. The residual semi-solid was triturated with warm hexane (200 mL) and the precipitated triphenylphosphine oxide removed by filtration. The filtrate was evaporated *in vacuo* to give crude **6**, purified by distillation, bp. 92-94°/0.5 mm, to yield 71 g (87%), shown by glc to be a 95:5 mixture of *cis/trans* isomers. The IR spectrum of **6** had a strong band at 980 cm^{-1} thus confirming the presence of *trans* alkene.[8] ^1H NMR: δ 5.20 (m, 2H), 3.66 (s, 3H), 2.26 (t, 2H), 1.6(m, 2H), 1.29 (broad s,17H), 0.84 (d, 6H).

13-Methyltetradecanoic Acid (8).- To a solution of **6** (138 g, 0.55 mole) in 95% EtOH (100 mL) contained in a 500 mL pressure bottle was added PtO_2 (0.5 g). Hydrogenation was carried out on a Parr hydrogenation apparatus at 45 psi H_2 pressure for 4 hrs. Glc indicated complete conversion to methyl 13-methyltetradecanoate (**7**) in this time period. The catalyst was removed by filtration and the solvent was stripped from the product. The residue was distilled to give 132 g (94%) of methyl 13-methyltetradecanoate, bp. 105-107°/0.5 mm, lit.[9] bp. 118-119°/1 mm: ^{1}H NMR: δ 3.66 (s, 3H), 2.31 (t, 2H), 1.64 (p, 2H), 1.52 (h, 1H), 1.29 (m, 21H), 1.16 (m, 2H), 0.86 (d. 6H); GCMS (m/e$^+$, 70 ev): 256(M^+), 225 (M^+-OCH_3), 213 (M^+-C_3H_7), 199 (M^+-C_4H_9), 74 (M^+-$C_{13}H_{26}$). Methyl ester **7** (128 g, 0.5 mole) in 90% EtOH (500 mL) was saponified with KOH (44.7 g, 0.68 mole) at reflux for 6 hrs. The reaction was cooled, diluted with H_2O (1 L), acidified with conc. HCl to pH 1 and extracted with ether (3x250 mL). The organic layers were combined, washed with H_2O (4x200 mL), dried over anhy. Na_2SO_4 and the solvent removed *in vacuo* to leave a cream colored solid. Recrystallization from acetone (1 g/5 mL) at 0° gave pure **8**, 113 g (88%), mp. 51.5-52°, lit.[10] mp. 52-52.5°.

Tri-(13-methyltetradecanoyl)glycerol 9.- Into a 1 L round bottom flask was placed anhy. glycerol (15.9 g, 0.166 mole), 13-methyltetradecanoic acid **8** (126 g, 0.52 mole) and *p*-toluenesulfonic acid (1 g) as catalyst. The flask was connected to a vacuum pump equipped with a water bulb trap and an ice water condenser. The mixture was heated to 155° under a vacuum of 45-50 mm Hg for 3 hrs at which time tlc analysis indicated complete reaction. The mixture was cooled to room temp., diluted with toluene (100 mL) and applied to a chromatographic column (5 x 90 cm) packed with silica gel (8 g per g of crude **9**) in toluene. The column was eluted with 10% ether-toluene (100 mL fractions) that were monitored by tlc. Fractions that contained only triglyceride were combined and solvent removed to give an oil that crystallized on standing. Recrystallization from acetone (1 g/4 mL) at -20° gave 104 g (82%) of pure triglyceride **9**, mp. 30.5-31°. ^{1}H NMR δ , 0.90 (d, 18 H), 1.16 (m, 6H), 1.31 (m, 63H), 2.35 (t, 6H), 4.25 (m, 2H), 5.3 (m, 1H); GCMS (direct probe, 70 ev): (m/e): 765 (M^+), 523 (M^+-RCO_2), 509 (M^+-RCO_2CH_2), 353, 299, 225 (RCO^+).

Acknowledgement.- We thank Dr. R. Dudley and Mr. E. Piotrowski for their assistance in obtaining the ^{1}H NMR and GCMS spectra respectively.

REFERENCES

1. E. Oldfield, M. Meadows, D. Rice and R. Jacobs, *Biochemistry*, **17**, 2727 (1978); b) H. J. Shafer, *Chem. Phys. Lipids*, **24**, 321 (1979); c) R. A. Klein, D. Halliday and P. G. Pettet, *Lipids*, **15**, 572 (1980).

2. H. J. J. Pabon, D. Van Der Steen and D. A. Van Dorp, *Recl. J. R. Neth. Chem. Soc.*, **84**, 1319 (1965); *Chem. Abs.*, **64**:3342g (1965); b) H. Rakoff and E. A. Emken, *Chem. Phys. Lipids*, **31**, 2155 (1982).

3. I. Gosney and A. G. Rowley, "Stereoselective Syntheses of Alkenes *via* the Wittig Reaction", in Organophosphorous Reagents in Organic Synthesis, p 17 (J. I. Cadogan, ed.) Academic Press, (1979); b) Y. Le Bigot, N. Hajjaji, I. Rico, A. Lattes, M. Delmas and A. Gaset, *Syn. Commun.*,

15, 495 (1985).; c) H. Rakoff, *Prog. Lipid Res.*, **21**, 225 (1982).

4. H. Rakoff and E. A. Emken, *J. Labelled Compd.*, **XV**, 233 (1978).

5. B. E. Maryanoff and B. A. Duhl-Emswiler, *Tetrahedron Lett.*, **22**, 4185 (1981); *J. Am. Chem. Soc.*, **107**, 217 (1985).

6. Reference to brand or firm name does not constitute endorsement by the U.S. Department of Agriculture over others of a similar nature not mentioned.

7. L. D. Bergelson, V. A. Vaver, A. A. Bezzubov and M. M. Shemyakin, *Zh. Obsch. Khim.*, **32**, 1807 (1962).

8. C. Paquot, "Determination of Isolated *trans*-Unsaturated Compounds by Infrared Spectroscopy", in IUPAC Standard Methods for the Analysis of Oils, Fats and Derivatives, Pergamon Press, (1979).

9. A. Seher and R. Kuhnast, *Fette Seifen Anstr.*, **67**, 657 (1965); *Chem. Abs.*, **64**:6487 b (1965).

10. G. Grimmer and J. Jacob, *Biochem. Z.*, **34**, 315 (1965).